Stroke Caused by Atherosclerosis of the Major Intracranial Arteries

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Abstract: **Our goal in this review is to discuss the pathophysiology, diagnosis, and treatment of stroke caused by atherosclerosis of the major intracranial arteries. References for the review were identified by searching PubMed for related studies published from 1955 to June 2016 using search terms intracranial stenosis and intracranial atherosclerosis. Reference sections of published randomized clinical trials and previously published reviews were searched for additional references. Intracranial atherosclerotic disease is a highly prevalent cause of stroke that is associated with a high risk of recurrent stroke. It is more prevalent among blacks, Hispanics, and Asians compared with whites. Diabetes mellitus, hypertension, metabolic syndrome, smoking, hyperlipidemia, and a sedentary lifestyle are the major modifiable risk factors associated with intracranial atherosclerotic disease. Randomized clinical trials comparing aggressive management (dual antiplatelet treatment for 90 days followed by aspirin monotherapy and intensive management of vascular risk factors) with intracranial stenting plus aggressive medical management have shown medical management alone to be safer and more effective for preventing stroke. As such, aggressive medical management has become the standard of care for symptomatic patients with intracranial atherosclerotic disease. Nevertheless, there are subgroups of patients who are still at high risk of stroke despite being treated with aggressive medical management. Future research should aim to establish clinical, serological, and imaging biomarkers to identify high-risk patients, and clinical trials evaluating novel therapies should be focused on these patients. (*Circ Res*. 2017;120:502-513. DOI: 10.1161/CIRCRESAHA.116.308441.)**

Key Words: arteries ■ aspirin ■ diabetes mellitus ■ hypertension ■ risk factors ■ stroke

Atherosclerosis in major intracranial arteries leads to changes ranging from minor wall thickening to hemodynamically significant luminal stenosis and is one of the most common causes of stroke worldwide.[1] Intracranial atherosclerotic disease (ICAD) may occur concomitantly with systemic atherosclerosis involving other arterial beds, such as extracranial, coronary, or peripheral arteries, or may occur in isolation.[2,3] The middle cerebral arteries (MCAs) are the most common site, followed by the basilar artery, the internal carotid arteries, and the intracranial vertebral arteries.[4,5] ICAD is highly prevalent in black, Asian (China, Japan, South Korea, and India), and Hispanic populations.[1] As these populations

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Nonstandard Abbreviations and Acronyms

BIOSIS	Biomarkers of Ischemic Outcomes in Intracranial Stenosis
CHANCE	Clopidogrel in High-Risk Patients With Acute Nondisabling Cerebrovascular Events
CHARISMA	Clopidogrel for High Atherothrombotic Risk and Ischemic Stabilization, Management, and Avoidance
CHIASM	Characterization of Intracranial Atherosclerotic Stenosis Using High-Resolution MRI
CLAIR	Clopidogrel Plus Aspirin for Infarction Reduction
EC-IC	Extracranial to Intracranial
EXPRESS	Existing Preventive Strategies for Stroke
ICAD	intracranial atherosclerotic disease
INR	international normalized ratio
MCA	middle cerebral artery
MRA	magnetic resonance angiography
MRI	magnetic resonance imaging
PROGRESS	Perindopril Protection Against Recurrent Stroke Study
PTAS	percutaneous transluminal angioplasty and stenting
ROCAS	Regression of Cerebral Artery Stenosis
SAMMPRIS	Stenting and Aggressive Medical Management for Preventing Recurrent Stroke in Intracranial Stenosis
SONIA	Stroke Outcomes and Neuroimaging of Intracranial Atherosclerosis
SPARCL	Stroke Prevention by Aggressive Reduction in Cholesterol Levels
TCD	transcranial Doppler
TIA	transient ischemic attack
TOSS-2	Trial of Cilostazol in Symptomatic Intracranial Stenosis 2
VERiTAS	Vertebrobasilar Flow Evaluation and Risk of Transient Ischemic Attack and Stroke
VISSIT	Vitesse Intracranial Stent Study for Ischemic Therapy
WARSS	Warfarin–Aspirin Recurrent Stroke Study
WASID	Warfarin–Aspirin Symptomatic Intracranial Disease

are major drivers of global population growth, the global stroke burden from ICAD is expected to rise over time.

Clinical trials in the last decade have improved our understanding of the high stroke recurrence rate in ICAD, risk factors, and neuroimaging biomarkers associated with recurrence, as well as ushered in therapeutic changes. In this study, we review the epidemiology, risk factors, pathophysiology, diagnosis and management of ICAD.

Epidemiology

Twenty to 40 per 100 000 people worldwide are estimated to suffer an ICAD-related ischemic event.[6] Examination of intracranial arteries during autopsy identified severe ICAD in 43% among aged 60 to 69, 65% among 70 to 79, and 80% among those ≥80 years.[7] Eighty-two percent Dutch patients >55 years had intracranial internal carotid artery calcification on computer tomographic scans in the population-based Rotterdam Study.[8] Among French patients who suffered fatal ischemic stroke, autopsy found ICAD in 62.2%, with 43% of these patients having luminal stenosis >30%.[9] In this study, ICAD with >30% stenosis was thought to be causally related to the fatal infarct in ≈6%.[9] In addition, ICAD is also associated with concomitant extracranial stenosis or atrial fibrillation in 10% to 20% patients.[10,11] ICAD and atrial fibrillation are both age-related and share risk factors.[12] In a Korean study of patients with nonvalvular atrial fibrillation who underwent cerebral angiograms, concomitant ICAD with >50% luminal stenosis was found in 29.6% patients.[11] Among asymptomatic predominantly white patients referred for carotid Doppler, transcranial Doppler (TCD) identified ICAD in 13%.[13] Among asymptomatic Chinese patients, TCD screening detected intracranial stenosis in 6.9% to 12.6%.[14,15]

ICAD is more prevalent among blacks and Asians when compared with white patients.[16–21] In the multiethnic Northern Manhattan study, prevalence of symptomatic ICAD was 3, 13, and 15 per 100 000 among white, Hispanic, and black subjects[22] and was responsible for 9%, 15%, and 17% of strokes among these groups.[22] In a postmortem study of subjects in China, 30% to 50% were found to have ICAD with >50% luminal stenosis.[18] Among asymptomatic Chinese patients with diabetes mellitus, TCD detected MCA ICAD in 20.6%.[23] Similarly, a magnetic resonance angiography (MRA) study evaluating asymptomatic ICAD among Japanese population showed 15% prevalence.[24]

Among blacks, the high prevalence of ICAD is partly attributed to the disproportionately high prevalence of hypertension, diabetes mellitus, and hyperlipidemia.[25,26] The Japanese population has a high burden of hypertension but low prevalence of hyperlipidemia.[27] Rates of hypertension, diabetes mellitus, and hyperlipidemia are comparable to whites in the Chinese population.[28] Genetic susceptibility and environment are also thought to play a role.

Risk Factors for ICAD

Risk factors associated with ICAD may be divided into modifiable and nonmodifiable (Table 1). Hypertension, diabetes mellitus, and age were independently associated with both symptomatic and asymptomatic ICAD on TCD in Korean, Japanese and white patients.[29–31] In a Spanish cohort, diabetes mellitus and metabolic syndrome conferred a higher risk for ICAD than extracranial atherosclerotic disease in asymptomatic patients.[32] The association between diabetes mellitus and ICAD is partly mediated by coexistent hypertension and hyperlipidemia.[33] Higher hemoglobin A1c does not correlate with severity of ICAD,[34] but diabetes mellitus remains an independent risk factor.[34,35] In the WASID trial (Warfarin–Aspirin Symptomatic Intracranial Disease), mean systolic blood pressure >140 mm Hg and mean cholesterol concentration >200 mg/dL during the follow-up in the trial were associated with an increased risk of recurrent stroke.[36]

Up until recently moderate or heavy intensity physical activity had only been associated with a decreased risk of ischemic stroke in patients with heterogeneous causes of stroke[37]; however, the recently completed SAMMPRIS trial (Stenting and Aggressive Medical Management for Preventing Recurrent Stroke in Intracranial Stenosis) showed that exercise during follow-up in the trial was strongly associated with a lower risk of stroke in subjects in the medical group in the trial.[38] Lipoprotein biomarkers of ICAD progression were studied in data from the TOSS-2 trial (Trial of Cilostazol in Symptomatic Intracranial Stenosis 2) on 230 patients with symptomatic stenosis of MCA and basilar artery. High apolipoprotein B/A-I

Table 1. Literature Review

The references used for this review were identified by searching PubMed for related studies published from 1955 to June 2016. The search terms intracranial stenosis and intracranial atherosclerosis were used, which yielded 5578 and 11 350 articles, respectively. English articles were reviewed. Abstracts were read by 1 author (C.B.), and relevant studies were screened in. Reference sections of published randomized clinical trials (304 articles) and previously published reviews (635 articles) were searched for additional references. The other author (M.I.C.) added relevant additional references after review.

was associated with progression of stenosis on MRA, whereas increase in high-density lipoprotein cholesterol and reduction of remnant lipoprotein cholesterol were associated with nonprogression of stenosis.[39] In a study among 231 Korean patients with acute (<7 days) ischemic stroke, patients with intracranial atherosclerosis had a decreased serum adiponectin level, when compared with patients with cardioembolic stroke or extracranial atherosclerosis.[40] Increased lipoprotein(a), C-reactive protein, and plasminogen activator inhibitor-1[41] are other biomarkers associated with the progression of ICAD. In an autopsy study, carriers of the glutathione S-transferase omega-1 Asp/Asp genotype were found to have more severe and widespread intracranial atherosclerosis than noncarriers, although there was no effect of the polymorphism on small vessel disease severity.[42] Among 40 Spanish patients with ischemic stroke secondary to ICAD, a higher endostatin/vascular endothelial growth factor ratio was associated with higher severity of stenosis (odds ratio, 15.7; confidence interval, 2.2–112.3), as well as a higher risk of recurrent events over a 13-month follow-up (hazard ratio, 7.24; confidence interval, 1.6–33.8).[43] This association is nonspecific though and has also been seen in chronic myocardial and limb ischemia.[43] No genetic polymorphisms specifically related to ICAD have been elucidated in genome-wide association studies.[44] T(-344) C polymorphism of the renin–angiotensin–aldosterone system-associated gene and TT genotype of phosphodiesterase 4D has been associated with ICAD but not with extracranial atherosclerosis.[45]

Pathophysiology

The first areas of intimal necrosis in intracranial arteries occur 1 or 2 decades earlier than the first fibromuscular plaques and the first fatty streaks.[46] Appearance of atherosclerotic plaques in basilar artery precedes those in cerebral arteries in the anterior circulation (Figure).[47] Intimal and adventitial proliferative fibrosis is more common in intracranial arteries than lipid infiltration.[48] A postmortem histological comparison of MCA plaques found that the degree of luminal stenosis, the percentage of the plaques containing >40% lipid area, and the prevalence of intraplaque hemorrhage, neovasculature, and thrombus were higher in those plaques associated with infarct.[49] Calcium deposits in the degenerated media are less common in intracranial arteries when compared with coronary arteries.[2]

Intracranial arteries lack an external elastic lamina.[50] This, along with impaired complement regulation,[50] expression of ubiquitin proteasome conjugates, and nuclear factor κB[51] may explain plaque instability and susceptibility to inflammation in intracranial arteries.

Mechanisms of Stroke in ICAD

There are several possible mechanisms of ischemic stroke in ICAD: artery–artery embolism, hypoperfusion, and branch atheromatous disease.[52–54] These specific mechanisms may have different prognoses, recurrence rates, and response to medical or endovascular therapy.[55–57] Specific mechanisms may be inferred by determining infarct patterns on neuroimaging. The infarct patterns may be classified as follows[58]: (1) perforator pattern—subcortical infarcts in the territory of perforating arteries that arise at the site of the intracranial stenosis, (2) territorial pattern—infarcts located distal to the stenotic vessel (cortical, subcortical, or both) that are restricted to the territory supplied by that artery, (3) borderzone pattern—infarcts in the internal borderzone region (corona radiata or centrum semiovale) or the cortical borderzone region (between the MCA and the posterior cerebral artery or the MCA and the anterior cerebral artery) or both, and (4) mixed pattern—a combination of any of the above patterns. Artery-to-artery embolism or in situ thrombo-occlusion is the likely mechanism for the territorial pattern, occlusion of the origin of a perforator or multiple perforators at the site of the intracranial stenosis for the perforator pattern, hypoperfusion for a borderzone pattern, and a mixed mechanism for a mixed pattern of infarct.[58] In the WASID trial, the infarct patterns for the strokes that qualified subjects for the trial were territorial in 50.7%, perforator in 25%, mixed in 15.5%, and

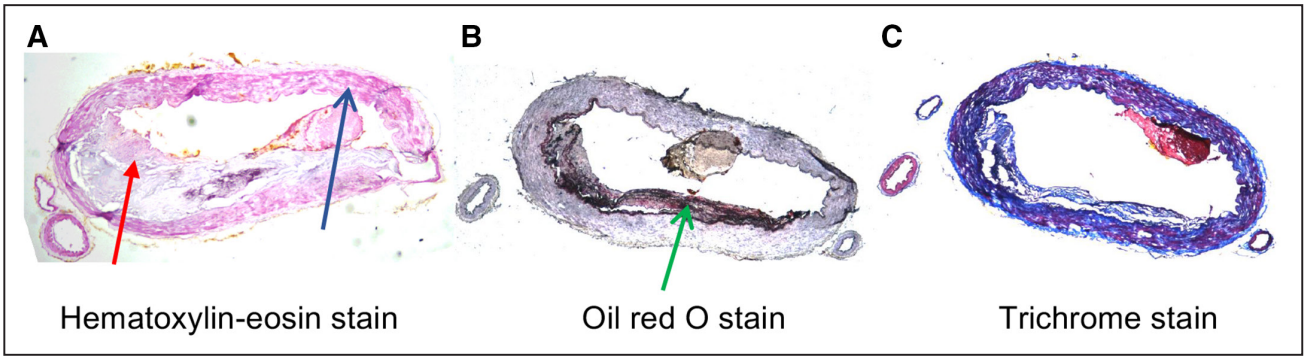

Figure. Histological cross-section of intracranial atherosclerosis in basilar artery. Image courtesy Dr Tanya Turan. Red arrow—fibrous tissue, blue arrow—vessel wall, and green arrow—lipid

borderzone in 8.8%.[58] Perforator infarcts were more common in the posterior circulation compared with the anterior circulation.[58] In the medical arm of SAMMPRIS trial, out of 101 patients with qualifying strokes in the territory of MCA or internal cerebral artery, the infarct patterns were considered predominantly borderzone in 53 (52.4%), predominantly territorial in 24 (23.8%), and perforator in 24 (23.8%). Patients who had borderzone infarcts as their qualifying stroke were more likely to have poor collaterals and had a higher risk of recurrent stroke.[59]

In a 9-center study performed in Korea, of the 657 patients with stroke secondary to ICAD, the infarct patterns were territorial in 65.3% (46.3% were considered secondary to artery-to-artery embolism, 19.0% were considered secondary to in situ thrombo-occlusion), perforator pattern in 21.0%, borderzone (hemodynamic) alone in 0.8%, and mixed in 12.9%.[60] The different frequencies of borderzone patterns of infarction among these 3 studies (WASID, SAMMPRIS, and the Korean study) are probably related to the fact that SAMMPRIS only enrolled subjects with ≥70% stenosis, whereas the other 2 studies enrolled subjects with ≥50% stenosis.

Diagnosis and Risk Stratification

Intracranial atherosclerotic stenosis can be diagnosed, quantified, and characterized by noninvasive neuroimaging and catheter angiography (Table 2). TCD, MRA, and computer tomographic angiography are the noninvasive modalities that offer safer, accessible, and less expensive methods of evaluating intracranial circulation than invasive catheter angiography. However, the accuracy of these modalities is less clearly outlined.

The SONIA trial (Stroke Outcomes and Neuroimaging of Intracranial Atherosclerosis)[62] was conducted in collaboration with the WASID trial to develop TCD and MRA cutoff points and assess their positive predictive value against the catheter angiography gold standard. TCD had a negative predictive value of 86% and a positive predictive value of 36% to detect a 50% to 99% stenosis.[62] Similarly, MRA (without contrast enhancement) had a negative predictive value of 91% and a positive predictive value of 59%. Thus, these modalities are a useful screening test to exclude intracranial arterial stenosis >50% but are unreliable to diagnose, quantify, or characterize ICAD (Table 3). There are some data to suggest that the sensitivity and specificity of TCD is higher in the anterior circulation, when compared with the posterior circulation.[63]

Computer tomographic angiography may be the most accurate of the noninvasive tests for diagnosing ICAD. In 1 study, computer tomographic angiography detected >50% stenosis with a sensitivity of 97%, specificity of 99.5%, positive predictive value of 93%, and negative predictive value of 99.8% compared with catheter angiography.[64]

Severity of stenosis and collateral flow status are important factors that correlate with the risk of stroke in patients with ICAD. Catheter angiography is needed for reliable quantification of luminal stenosis. Severity of stenosis is calculated as a ratio between the vessel diameter at the point of maximum stenosis and the diameter of the normal proximal artery[65] (sometimes, the distal artery or the feeding artery may be used).

In the WASID trial, risk of recurrent stroke increased with the severity of luminal stenosis.[66] Patients with >70% intracranial stenosis had almost double the risk of recurrent ipsilateral stroke when compared with those with <70% stenosis at 1 year (18% versus 7%–8%).[66] In patients with >70% stenosis in WASID, recurrent stroke risk further depended on the time interval between qualifying event and enrollment. Those who were enrolled early (<30 days) had much higher recurrent risk than those who were enrolled between 30 and 90 days after the qualifying events.[66] These data formed the basis for restricting enrollment in the subsequent SAMMPRIS trial to 70% to 99% stenosis and qualifying event within 30 days before enrollment. Importantly, the rate of stroke decreased significantly beyond 1 year of follow-up. For example, in subjects with 70% to 99% stenosis who had their qualifying event within 30 days before enrollment, the cumulative rate of stroke increased from 22.9% at 1 year to only 25% at 2 years, that is, only 2.1% additional patients experienced a stroke in the second year of follow-up.[66]

Why are patients with more severe stenosis at higher risk of stroke? One possible reason is that more severe stenosis is associated with distal hemodynamic compromise. In subjects with severe extracranial carotid stenosis, diminished vasomotor cerebrovascular reserve distal to the stenosis is thought to increase risk of ischemic stroke.[67] However, 1 study of subjects with intracranial carotid and MCA stenosis suggested that hemodynamic compromise may not correlate as strongly with risk of stroke/transient ischemic attack (TIA).[68] On the other hand, the extent of collateral flow, which correlates with the severity of intracranial stenosis,[69] was strongly associated with the risk of stroke in the WASID trial.[70] On baseline angiography in WASID subjects, collaterals were absent in 69%, slow or minimal in 10%, rapid but incomplete in 7%, complete but delayed in 11%, and rapid and complete in 4%.[69] For patients with >70% stenosis, absence of collaterals increased risk of recurrent stroke by 4.6×.[70] At 50% to 69% stenosis, poor collaterals increased stroke risk by 1.78× in WASID subjects.[70]

The presence of severe stenosis and poor collaterals does not necessarily prove that the final pathophysiologic mechanism of stroke is low distal flow because artery-to-artery embolism may also occur more frequently in this setting as well. Presence of microembolic signals detected by TCD monitoring as high-intensity transient signals in the symptomatic

Table 2. Risk Factors of Intracranial Atherosclerosis

Nonmodifiable Risk Factors	Modifiable Risk Factors
Age	Hypertension
Race (black, Hispanic, Chinese, Korean, Japanese, and Indian)	Diabetes mellitus
	Metabolic syndrome
Male sex	Smoking
Family history of stroke[15]	Hyperlipidemia: low-density lipoprotein, high-density lipoprotein, total cholesterol, β-lipoprotein, and apolipoprotein (a)
Radiotherapy[61]	
Decreased s-adiponectin[40]	
Glutathione S-transferase omega-1 gene polymorphism[42]	Plasma homocysteine
Plasma endostatin/vascular endothelial growth factor ratio[43]	Physical inactivity

Table 3. Advantages and Disadvantages of Different Diagnostic Modalities for Diagnosing Intracranial Arterial Stenosis

	Catheter Angiogram	CT Angiogram	MRA	Transcranial Doppler
Advantages	Best resolution, Assessment of flow dynamics, collaterals, plaque morphology	Fast, better than MRA in slow-flow states	No radiation, may be done in patients unable to get iodinated or gadolinium contrast	Emboli monitoring, dynamic monitoring possible, can assess vasomotor reserve, useful in vasospasm, sickle cell disease, no radiation
Limitations	Invasive, periprocedural stroke risk, groin hematoma	Contrast nephropathy, ionizing radiation, contraindicated in renal dysfunction, artifact with aneurysm clips, heavily calcified plaque	Takes longer, claustrophobia, contraindicated in pacemakers, some metallic implants, slow flow in vessel may seem as flow gap, may overestimate degree of stenosis	Operator dependent, temporal acoustic window may be absent/poor, assesses proximal segments of intracranial vessels only, unable to locate stenotic size accurately within vessel

CT indicates computer tomography; and MRA, magnetic resonance angiogram.

intracranial vessel territory increases with stenosis severity and also confers increased risk of recurrent stroke.[71] In patients with MCA stenosis, presence of microemboli within 3 days of stroke onset increased the risk of recurrent stroke/TIA >8-fold over the next year after controlling for confounders.[71]

High-resolution magnetic resonance imaging (MRI) sequences on a 3-T MRI scanner allow for characterization of plaque morphology and identification of high-risk plaque components such as intraplaque hemorrhage,[72] thin or ruptured fibrous cap,[73] and high lipid core scores.[74] Enhancement within the plaque with gadolinium contrast has been shown to correlate with fibrous cap rupture in histological specimens.[73] Detection of these findings has reliable inter-rater agreement for carotid plaques.[75] The National Institutes of Health–funded CHIASM study (Characterization of Intracranial Atherosclerotic Stenosis Using High-Resolution MRI) is currently underway to assess inter-rater agreement and association of high-risk plaque components with 1-year stroke risk.[75] Intravascular ultrasound can identify high-risk plaque components too, but its invasive nature makes routine use unlikely.[76]

Treatment

Antithrombotic Therapy: Anticoagulation Versus Aspirin

Anticoagulation was first used as treatment of ICAD in 1955 when warfarin was used to treat basilar artery stenosis.[77] A retrospective, multicenter study initially compared the efficacy of warfarin with aspirin in patients with symptomatic 50% to 99% intracranial stenosis between 1985 and 1991.[78] There were fewer vascular events in the warfarin group when compared with aspirin. On the other hand, the WARSS (Warfarin–Aspirin Recurrent Stroke Study), a multicenter, double-blind, randomized trial, that compared warfarin (target international normalized ratio [INR], 1.4–2.8) to aspirin 325 mg per day in subjects with heterogeneous causes of stroke found no difference in the rate of recurrent ischemic stroke, death, or major hemorrhage. The majority of qualifying strokes in WARSS were lacunar (1237 out of 2206). But, even in the subgroup of patients with large artery stenosis/occlusion, there was no difference seen between the 2 groups.[79]

The WASID trial was a multicenter, double-blind, randomized trial that compared warfarin (target INR, 2–3) versus aspirin (1300 mg/d) in patients with 50% to 99% intracranial stenosis with TIA or stroke within 90 days before enrollment. After enrolling 569 patients, the trial was halted because the warfarin arm had a significantly higher rate of major systemic hemorrhage and death. Over a mean follow-up of 1.8 years, the groups had the same rate of the combined primary end point of ischemic stroke, intracranial hemorrhage, and vascular death.[4] Recurrent ischemic stroke in the territory of the symptomatic vessel was also similar between the 2 groups. In the WASID trial, even subgroups that were previously thought to benefit with anticoagulation, such as more severe (70%–99%) stenosis, patients on antithrombotic therapy before the qualifying ischemic event and those with stenosis in multiple intracranial arteries did not derive a benefit from warfarin.[80,81] Although aspirin treatment in patients with basilar stenosis had a higher risk of any stroke or vascular death, this was not seen in patients with vertebral artery stenosis, and the rate of recurrent stroke in the basilar artery territory was comparable between the 2 groups as well, suggesting no overall benefit of warfarin over aspirin.[81] In the warfarin arm, percentage of time spent within the target INR was 63%, when compared with 94% compliance in the aspirin group.[4] INR <2 significantly increased risk of stroke, whereas INR >3 was associated with increased risk of hemorrhage.

A comparison of anticoagulation versus aspirin for lowering the risk of early recurrent stroke in subjects with acute (within 48 hours before enrollment) symptomatic large artery occlusive disease has also been evaluated in Asian subjects in the FISSTris trial.[82] Most of the subjects in this trial (342 out of 353) had ICAD. In this randomized, multicenter trial, subjects treated with the low-molecular-weight heparin nadroparin calcium or aspirin 160 mg per day had similar outcomes at 10 days.[82]

Antithrombotic Therapy: Other Antiplatelet Agents

Aspirin, clopidogrel, combination aspirin-extended release dipyridamole, cilostazol, and ticagrelor are the antiplatelet drugs that have been shown to be effective for the prevention of recurrent ischemic stroke in patients with noncardioembolic ischemic stroke or TIA. But, they have not been compared with placebo or each other in randomized trials specifically in patients with ICAD. The use of short-term dual antiplatelet therapy may be more effective in lowering the high early recurrence risk in patients with symptomatic ICAD when compared with

single therapy. In the CLAIR study (Clopidogrel Plus Aspirin for Infarction Reduction),[83,84] patients with ICAD with a stroke ≤7 days were randomized to receive aspirin (75–160 mg/d) or clopidogrel (300 mg load on day 1, followed by 75 mg/d) plus aspirin (75–160 mg/d). The dual therapy group had lower rate of microembolic signals (a known biomarker of high recurrent stroke risk in ICAD as described above) detected by TCD on days 2 and 7 than those on aspirin alone.

Further evidence that the combination of aspirin and clopidogrel may be more effective than aspirin alone for early secondary prevention of stroke comes from the CHANCE trial (Clopidogrel in High-Risk Patients With Acute Nondisabling Cerebrovascular Events) performed in China. CHANCE compared clopidogrel plus aspirin versus aspirin alone for reducing the 90-day risk of any stroke (ischemic or hemorrhagic) when initiated within 24 hours of symptom onset in high-risk patients with acute minor stroke or TIA.[85] CHANCE showed that the risk of stroke at 90 days was significantly lower in the combination antiplatelet arm, and a secondary analysis showed that subjects with ICAD may have particularly benefited from combination therapy.[86] Use of combination aspirin and clopidogrel is not recommended beyond 90 days because of increased risk of major hemorrhage as seen in the MATCH[87] trial and CHARISMA[88] trial (Clopidogrel for High Atherothrombotic Risk and Ischemic Stabilization, Management, and Avoidance), where long-term combination aspirin and clopidogrel was compared with clopidogrel and aspirin, respectively.

Cilostazol is an antiplatelet drug with vasodilatory properties. In a Korean multicenter, double-blind study,[89] patients with acute symptomatic stenosis in the M1 segment of MCA or the basilar artery as measured by MRA and TCD were randomized to combined cilostazol 200 mg per day and aspirin 100 mg per day or aspirin alone for 6 months. There was no stroke recurrence in both groups, and the progression of symptomatic ICAD on MRA was significantly lower in the combination therapy group. In a sequel trial,[90] the same entry criteria were used, and patients were randomized to combined aspirin (75–150 mg/d) plus cilostazol (100 mg twice daily) versus aspirin (75–150 mg/d) plus clopidogrel (75 mg/d). At 7 months, there was no significant difference in the progression of symptomatic ICAD on MRA. There was no significant difference with respect to new ischemic lesions on MRI as well (18.7% versus 12.0%)

Risk Factor Control

Hypertension, hyperlipidemia, diabetes mellitus, and smoking are modifiable risk factors of ICAD. In the randomized, multicenter PROGRESS (Perindopril Protection Against Recurrent Stroke Study), blood pressure lowering regimen of perindopril with/without indapamide reduced the risk of stroke during 4 years of follow-up.[35] The SPARCL trial (Stroke Prevention by Aggressive Reduction in Cholesterol Levels)[34] showed that low-density lipoprotein cholesterol <1.81 mmol/L was associated with a 28% reduction in stroke risk compared with a level >2.59 mmol/L over 4.9 years. However, neither of these trials were specific to patients with ICAD and included other stroke etiologies. Most of our understanding of the pivotal role of risk factor modification in ICAD management began with subanalyses in the WASID trial.[33,36,91] In WASID, subjects with a mean systolic blood pressure ≥140 mm Hg during a mean follow-up period of 1.8 years had a higher rate of stroke, MI, or vascular death (31% versus 18% in subjects with mean systolic blood pressure ≥140 mm Hg; P=0.005).[33] This dispelled the commonly held hypothesis at the time of maintaining high blood pressure in patients with intracranial stenosis. Total mean cholesterol >200 mg/dL during follow-up was also associated with a higher risk of stroke, MI, or vascular death (26% versus 19% in subjects with mean cholesterol <200 mg/dL; P=0.02).[36] In WASID, 31% of patients with a mean hemoglobin A1c ≥7% during follow-up had a stroke, MI, or vascular death compared with 20% patients with mean hemoglobin A1c <7%, but the increased risk was not statistically significant (P=0.20),[33] likely because of lack of power.

In the randomized, double-blind ROCAS study (Regression of Cerebral Artery Stenosis),[92,93] 132 Chinese patients with asymptomatic MCA stenosis and increased low-density lipoprotein cholesterol (3.00–5.00 mmol/L) were randomized to simvastatin 20 mg per day or placebo for 2 years. Although the evolution of MCA stenosis was not different between the 2 groups, the rates of progression of cerebral white matter lesions, subclinical brain infarcts, all-cause mortality, and any clinical events were significantly lower in the simvastatin-treated group.[92–94]

In WASID, risk factor control was done per usual standard of care. There was only a modest improvement in risk factor profiles such as cholesterol and smoking in the cohort during follow-up.[91] After the subgroup analyses revealed significant reduction in recurrent stroke risk with reduction in blood pressure and cholesterol, aggressive medical management was incorporated in SAMMPRIS.[91] This incorporated target systolic blood pressure <140 mm Hg (<130 mm Hg in diabetes mellitus patients) and low-density lipoprotein <70 mg/dL and the use of a lifestyle modification program. The lifestyle modification program incorporated a treatment plan for physical activity, nutrition, weight management, and tobacco cessation.[91]

Early initiation of risk factor modification after an ischemic event may also be important. In the prospective EXPRESS study (Early Use of Existing Preventive Strategies for Stroke)[95] which was nested within the Oxford Vascular Study, early initiation of the existing treatments after a minor stroke or TIA was associated with an 80% reduction in the risk of recurrent stroke over 3 months. Similarly, with early initiation of antiplatelet, antihypertensive, and statin drugs in the SOS-TIA study, the 90-day stroke rate was 1.24% as opposed to the 5.96% rate predicted from ABCD2 scores.[96] Both of these trials, however, were not specific to patients with ICAD.

Endovascular Therapy

Angioplasty began being considered as a potential therapeutic option in patients with ICAD in 1980s. It has usually been used when patients with >70% stenosis have ischemic events despite being on antithrombotic therapy. Almost all of the data on angioplasty in ICAD comes from retrospective, single-center, nonrandomized studies with heterogeneous entry criteria that have reported periprocedural stroke rates varying between <5% and as high as 50%.[97–107] Clinically unstable and recently symptomatic patients overall seem to have higher periprocedural complication rates. Most of these studies had short duration of follow-up.

A Cochrane review published in 2006[108] evaluated angioplasty with or without stent placement in ICAD and did not find any randomized controlled trials. There were 79

open-label case series with ≥3 cases. The procedure showed an overall perioperative rate of stroke of 7.9%, perioperative death of 3.4%, and perioperative stroke or death of 9.5%. The authors concluded that although feasible, the procedure carries a significant morbidity and mortality risk. There are no data comparing patients treated with angioplasty alone to those with intensive medical management.

Angioplasty has technical limitations such as dissection, immediate elastic recoil of the artery, and residual stenosis following the procedure and restenosis in the immediate to long term.

In 2005, just as WASID ended, the Food and Drug Administration approved the self-expanding Wingspan stent (Stryker Neurovascular) under) for use in patients with atherosclerotic intracranial arterial 50% to 99% stenosis who had experienced a TIA or stroke while receiving antithrombotic therapy. Subsequently, the multicenter National Institutes of Health–funded SAMMPRIS trial randomized patients with a TIA or nondisabling stroke within the previous 30 days that was attributed to 70% to 99% stenosis of a major intracranial artery to percutaneous transluminal angioplasty and stenting (PTAS) with the Wingspan stent plus aggressive medical management versus treatment with aggressive medical management alone.[5,109] After 451 of the planned 764 patients (59%) were randomized between November 2008 and April 2011, enrollment in the trial was halted because of a significantly higher rate of stroke or death within 30 days of enrollment among those in the angioplasty and stenting group compared with those treated with medical therapy alone (14% versus 6%). Of the strokes that occurred within 30 days in the PTAS group, 76% (25 out of 33) occurred within 1 day of the procedure, and the rest occurred within 7 days. Symptomatic intracranial hemorrhage occurred in 10 patients. There were 5 fatal strokes within 30 days. There were no hemorrhages in the medical management group.

The periprocedural rate of stroke in the PTAS group was higher than expected from previously published Wingspan registries.[110–112] The main cause of the early ischemic strokes was the occlusion of perforating vessels, more than half of which were in basilar artery territory. The hemorrhages were either subarachnoid hemorrhage (some of which were from wire perforation) or delayed intraparenchymal hemorrhage attributed to reperfusion.[55] Risk factors significantly associated with periprocedural ischemic events were basilar artery stenosis, diabetes mellitus, older age, and nonsmoking status (smoking increases conversion of clopidogrel to its active metabolite), whereas risk factors associated with periprocedural intracranial hemorrhages included high percentage of stenosis and clopidogrel load associated with an activated clotting time above the target range.[113] A post hoc analysis evaluating site and operator experience concluded that the increased periprocedural risk in SAMMPRIS was not because of operator inexperience.[114] When compared with the Wingspan registries,[110–112] the higher severity of stenosis and the earlier window of treatment after an ischemic event (30 days) might have increased the periprocedural risk of PTAS in SAMMPRIS. Also, there was a more rigorous outcome adjudication process in SAMMPRIS.

At 1 year, the rate of stroke or death in the PTAS group was 20%, when compared with 12% in the medical management arm. At the end of the 32-month follow-up, the rate of primary outcome events continued to remain significantly higher for the PTAS group compared with the medical management group (23% versus 15%).[109] Although these long-term differences were largely driven by the 30-day outcomes, the benefit was sustained over time because the rates of stroke and death beyond 30 days were similar between the 2 groups.

A post hoc analysis from the SAMMPRIS trial focused on identifying patient characteristics associated with a high risk of recurrent stroke despite aggressive medical management. This analysis showed that an old infarct in the territory of the stenosis on baseline brain imaging, a new stroke presentation, and the absence of statin use at enrollment were independently associated with a high risk of recurrent stroke.[115] These features will be useful for selecting high-risk patients for future clinical trials evaluating alternative therapies for intracranial stenosis.

In January 2015, based on the results of SAMMPRIS, the United States Food and Drug Administration changed the humanitarian device exemption approval for the use of the Wingspan stent for patients who have had ≥2 strokes despite aggressive medical management; whose most recent stroke occurred >7 days before planned treatment with Wingspan; who have 70% to 99% stenosis because of atherosclerosis of the intracranial artery related to the recurrent strokes; and who have made good recovery from their previous strokes and have a modified Rankin score of ≤3 before Wingspan treatment.

The VISSIT trial (Vitesse Intracranial Stent Study for Ischemic Therapy), initiated soon after the start of SAMMPRIS, was an industry-funded randomized trial that had similar entry criteria.[116,117] VISSIT tested the PHAROS Vitesse balloon-expandable neurovascular stent system (Codman Neurovascular, Raynham, MA), as opposed to the self-expanding Wingspan stent used in SAMMPRIS. Medical therapy in VISSIT had similar targets as SAMMPRIS, except the low-density lipoprotein cholesterol target was <100 mg/dL as opposed to <70 mg/dL in the latter. Enrollment in VISSIT was halted for futility after 112 patients out of a planned 250 patients were enrolled. The 30-day rate of ischemic stroke or TIA was much higher in patients in the stent group (24.1% versus 9.4%). Intracranial hemorrhage within 30 days occurred in 8.6% in the stent group versus none in the medical arm. At 1 year, 36.2% in the stent group had a stroke or TIA, against 15.1% in the medical group.

Thus, evidence from SAMMPRIS and VISSIT trials does not support endovascular therapy in patients with ICAD. This is true even in high-risk subgroups because patients with the highest risk of stroke on medical therapy were also at the highest risk for stroke from stenting.[109,118]

Surgical Therapy

Extracranial to intracranial bypass surgery was studied as a therapeutic option for patients with symptomatic intracranial stenosis in the 1980s. The EC-IC bypass trial (Extracranial to Intracranial),[119] published in 1985, was an international, prospective, multicenter, randomized trial that compared extracranial to intracranial bypass (superficial temporal artery to the MCA) with medical therapy against medical therapy alone

in patients with extracranial carotid occlusion or intracranial carotid or MCA stenosis. Over a 55-month follow-up, surgery did not lower the rate of stroke compared with medically treated patients and was associated with a worse outcome in patients with MCA stenosis.[119] After the conclusive results of the trial, extracranial to intracranial bypass surgery ceased to remain a therapeutic option for treatment for the prevention of stroke in patients with symptomatic anterior circulation ICAD. A case series described superficial temporal to superior cerebellar artery bypass for vertebrobasilar insufficiency, but there was a high complication rate.[120]

Future Directions

Future research should focus on clinical characteristics, serological, or imaging biomarkers to identify high-risk patients with ICAD who are likely to fail medical therapy. Several noninvasive imaging modalities offer the ability to detect markers that allow additional risk stratification in ICAD beyond severity of stenosis. The importance of collaterals on catheter angiography, microembolic signals on TCD, impaired vasomotor reactivity, and high-risk features on high-resolution MRI such as intraplaque hemorrhage, thin or ruptured fibrous cap, and high lipid core scores has been discussed in the Diagnosis section.

Fractional flow reserve is an index that measures pressure proximal and distal to a stenosis to calculate the pressure gradient across it and determine its hemodynamically significance.[121–123] The measurement can be made invasively using an endovascular catheter or using MRA. Fractional flow reserve–guided endovascular revascularization strategy is popular in coronary intervention.[122] Time-of-flight MRA signal intensity correlates with blood flow velocity. Comparison of the signal intensity on time-of-flight MRA proximal and distal to a symptomatic intracranial stenosis may be a reasonable measure of fractional flow reserve associated with the stenosis. A post hoc analysis of patients in the WASID and SONIA trials suggests that patients with distal:proximal signal ratios of <0.9 on time-of-flight MRA are at a higher risk of stroke than are those with ratios of ≥0.9.[121] Recently, a Chinese feasibility study demonstrated that mean trans-stenotic pressure gradients can be safely and easily measured with a 0.014-inch fluid-filled guidewire in intracranial large arteries.[123]

Quantitative MRA is a technique that combines time-of-flight and phase-contrast MRA techniques to derive vessel-specific volumetric flow rates. The recently published VERiTAS study (Vertebrobasilar Flow Evaluation and Risk of Transient Ischemic Attack and Stroke)[124,125] showed that distal flow status determined using quantitative MRA is robustly associated with risk for subsequent stroke in patients with symptomatic atherosclerotic vertebrobasilar occlusive disease.

The BIOSIS study (Biomarkers of Ischemic Outcomes in Intracranial Stenosis)[126] affiliated with SAMMPRIS assessed whether inflammatory and endothelial cell biomarkers are predictors of stroke in the territory of the stenotic artery in SAMMPRIS patients and found that elevated levels of PAI-1 and hsCRP, as well as low circulating progenitor cells, were associated with increased risk of recurrent stroke.

When appropriate biomarkers have been established and validated for the identification of patients with ICAD who are at high risk of stroke despite aggressive medical therapy, alternative therapies should be compared with aggressive medical therapy in these patients. For any new endovascular therapy to prove beneficial, the rate of periprocedural stroke will need to be reduced substantially. Angioplasty alone with newer generation catheters may be safer than stenting because of the lower risk of distal wire perforation and the lower risk of thromboembolism.[127] The smaller profile of angioplasty balloons compared with stent-bearing catheters may cause less ostial occlusion of perforators by snow plowing of plaque. Currently, there are no prospective, multicenter studies of angioplasty alone in symptomatic ICAD.

Surgical augmentation of collateral flow distal to an intracranial stenosis may be achieved with encephaloduroarteriosynangiosis,[128] where donor arteries (superficial temporal artery and middle meningeal arteries) are placed in close proximity to the dural and cortical arteries distal to the intracranial stenosis, which over time leads to a network of collaterals between the donor artery and the adjacent superficial brain vessels without a surgical anastomosis.

Ischemic preconditioning is another potential treatment to reduce recurrent stroke risk in ICAD, which likely works by improving cerebral perfusion and reducing oxidative stress.[129] A small randomized trial compared upper limb ischemic preconditioning with usual care in patients with symptomatic intracranial stenosis.[130] Upper limb preconditioning involved brief repetitive cycles of occluding both brachial arteries with a blood pressure cuff twice daily for 300 days. They found a substantially lower rate of stroke at 300 days in the upper

Table 4. Summary of Findings

ICAD is a highly prevalent cause of stroke.
It is more prevalent among black, Hispanic, and Asian patients when compared with white patients.
Diabetes mellitus, hypertension, metabolic syndrome, smoking, and hyperlipidemia are the major modifiable risk factors associated with ICAD.
Risk of stroke recurrence among patients with symptomatic ICAD is high and variable.
Aggressive medical management, with antiplatelet medications and risk factor modification, is a treatment of choice.
Randomized clinical trials comparing intracranial stenting with aggressive medical management to aggressive management alone did not show benefit of stenting.
Despite aggressive medical therapy, a subgroup of patients has high recurrent stroke risk.
Future research should aim to establish clinical, serological, and imaging biomarkers to identify patients with high recurrent stroke risk, and clinical trials evaluating novel therapies should be focused on these patients.

ICAD indicates intracranial atherosclerotic disease.

limb ischemic preconditioning group (7.9% versus 26.7%; $P<0.01$).[130] This may become a viable therapeutic option for patients with ICAD if the remarkable results of this small study can be validated in a larger multicenter randomized trial.

In WASID, when the INR was maintained between 2 and 3, the ischemic stroke and myocardial infarct rates in the warfarin arm were lower, and the major hemorrhages were few.[4] With novel oral anticoagulants, where anticoagulation status is easier to sustain, a revisiting of anticoagulation for the treatment of intracranial stenosis may be worthy of further study.

Conclusions

ICAD is a highly prevalent cause of stroke. Aggressive medical management with antiplatelet therapy and risk factor control is the treatment of choice (Table 4). However, a subgroup of patients with intracranial stenosis fails aggressive medical therapy. Future research should aim at establishing clinical, serological, and imaging biomarkers that can identify high-risk patients. In addition, there is an urgent need to develop novel therapies to lower the risk of stroke in these high-risk patients.

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